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Designing group dose-response studies in the presence of transmission

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ABSTRACT

Dose-response studies are used throughout pharmacology, toxicology and in clinical research to determine safe, effective, or hazardous doses of a substance. When involving animals, the subjects are often housed in groups; this is in fact mandatory in many countries for *social animals*, on ethical grounds. An issue that may consequently arise is that of unregulated between-subject dosing (transmission), where a subject may *transmit* the substance to another subject. Transmission will obviously impact the assessment of the dose-response relationship, and will lead to biases if not properly modelled. Here we present a method for determining the optimal design – pertaining to the size of groups, the doses, and the killing times – for such group dose-response experiments, in a Bayesian framework. Our results are of importance to minimising the number of animals required in order to accurately determine dose-response relationships. Furthermore, we additionally consider scenarios in which the estimation of the amount of transmission is also of interest. A particular motivating example is that of *Campylobacter jejuni* in chickens. Code is provided so that practitioners may determine the optimal design for their own studies.

1. Introduction

A group dose-response experiment involves exposing subjects to a range of doses of a substance (for example, an infectious agent, or bacteria or a drug) and measuring their responses (for example, if they became colonised) [4]. These experiments are routinely used to characterise the relationship between the dose of a substance and the response in a subject, known as the *dose-response relationship*.

Studies of this type have been widely used throughout pharmacology [27], toxicology [5] and in clinical trials [3], and methods for characterising the dose-response relationship developed [28]. However, a recent study by Conlan et al. noted a potential issue with such analyses when considering infectious agents [9]: in some cases, subjects may *transmit* their dose to other subjects, hence complicating the analysis. The motivating example is of *Campylobacter jejuni* in chickens.

The *Campylobacter* genus of bacteria is the most common cause of food-borne diarrhoeal disease in developed and developing countries – surpassing *Salmonella* and *Shigella* spp. [14]. Group dose-response experiments with *C. jejuni* in chickens are a useful tool in understanding the dose-response and transmission characteristics of the bacteria, allowing sensible measures to be put in place to contain, or eradicate, the infection in livestock used for human consumption. Chickens are social animals, and thus ethically are required to be co-housed [2]. Conlan et al. [9] noted that previous statistical analyses of the dose-response characteristics of *C. jejuni* in chickens had neglected the potential for transmission between co-housed subjects – resulting in incorrect estimation of the dose-response relationship.

The presence of transmission in these experiments leads to an "all-or-nothing" response if the subjects are observed too late – that is, once at least one subject is infected within a group, transmission to the initially uninfected chickens leads to more chickens being colonised than is representative of the administered dose. This yields a lower estimated ID_{50} (i.e., the dose required to infect 50% of the population, on average), and steeper slope-at-half-height – common statistics used to characterise dose-response curves [9]. To limit between-subject dosing, one might attempt to sample the chickens after a very short period of time following initial dosing. However, there exists a latent period between a chicken being challenged and it becoming colonised (i.e., it presenting its response), thus this also provides inaccurate assessment of the number of colonised subjects. Finally, a chicken is "observed" via post-mortem caecal sampling, meaning that only one observation of each subject is possible.

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Studies of this form – grouped dose-response experiments with the potential for between-subject dosing – are common, and given the ethical, financial and physical constraints associated with such studies, determining their optimal experimental design in order to obtain the most information about the dose-response relationship is important. One must consider the allocation of the number of subjects to groups, possibly different doses, and the associated time(s) to observe the process, in order to gain the most information about the dose-response relationship. In particular, using these optimal design tools, we can quantify the trade-off in information between allocating many individuals to few groups (doses), or few individuals to many groups (doses). We furthermore give consideration to scenarios in which the estimation of the transmission rate is also of interest – highlighting the potential for these tools to inform design of experiments where the purpose is understanding the transmission dynamics of a pathogen (e.g., avian influenza as in [26]).

We work within a Bayesian framework, allowing for use of prior information concerning the various components of the dose-response study, and transmission dynamics. Our method involves a novel continuous-time Markov chain model for the dynamics within such a study, combined with recently-developed methods for Bayesian optimal experimental design [20,21]. `MATLAB` code is provided so that practitioners may determine the optimal design for their own studies.

2. Methodology

2.1. Modelling of group dose-response experiments

The first step in determining the optimal experimental design for these experiments is determining suitable models to represent the dynamics amongst a group of subjects. In determining a suitable model, we must ensure we account for the experimental aspects we wish to determine as part of our optimal designs. First and foremost, we are interested in the optimal doses to allocate to subjects in order to gain the most information about the dose-response relationship. Hence, we must represent the dose-response relationships we believe are possible given the substance and subjects being studied. This is achieved by specifying a suitable prior distribution for the model parameters, which results in a range of dose-response curves we believe may eventuate from the experiment (examples given in Section 3).

We must also determine when to observe the process, to measure the response – in this example, we count the number of infectious chickens in each group (i.e., our data is the number of infectious individuals in each group). There are three important considerations when determining the optimal observation time for these group dose-response experiments. First, observation here is assumed to involve killing the subject; hence, we have only one observation for each subject. Second, transmission may occur which may in turn increase the number of colonised subjects we observe for a given dose, thus skewing the dose-response relationship to appear steeper, and reducing the estimate of the ID_{50} [9]. Hence, this suggests we should observe the process early enough in order to mitigate transmission. However, the earlier observation time due to transmission is in direct competition with the third and final consideration: the latent period. That is, there is a delay between exposure to a dose (say via injection, or ingestion) and colonisation. Thus, in determining the optimal observation time, we must allow sufficient time for the subject to pass through this latent period, but still observe the process early enough to ensure that there has not been significant amounts of transmission between subjects. With regards to the design, we choose one dose and observation time for all chickens within a group – that is, each chicken within a group receives an identical dose, and is killed at the same time.

In order to cover these three important aspects – the dose-response relationship, a latent period, and transmission – we propose a continuous-time Markov chain model to incorporate each of these stages. We use the beta-Poisson model for the probability of infection, P_{inf}, for a subject given dose D. That is,

$$P_{\text{inf}}(D;\alpha,\delta) \approx 1-\left(1+\frac{D}{\delta}\right)^{-\alpha}. \tag{1}$$

This follows as the approximation to the hypergeometric model used by Conlan et al. [9] – suitable when $\delta >> \max(\alpha, 1)$. Common statistics used to characterise a dose-response relationship are the ID_{50} and the Slope-at-half-height (SHH). The ID_{50} represents the dose required to infect 50% of the population, and the slope-at-half-height is a measure of the susceptibility of the host to the pathogen [9]. The ID_{50} and SHH can be evaluated with respect to α and δ as follows:

$$\text{ID}_{50} = \delta(2^{1/\alpha}-1), \qquad \text{and,} \qquad \text{SHH} = \frac{\log(10)}{2}\alpha\left(1-\left(\frac{1}{2}\right)^{1/\alpha}\right).$$

Note that the slope-at-half-height is independent of δ.

The model we consider takes into account both the latent period of infection, as well as transmission between subjects. We propose a SE_kI Markov chain epidemic model, where: subjects begin the process as healthy; then, the subjects move into either the (first, of k) exposed class (with probability P_{inf}, i.e., they are colonised by the design dose), or the susceptible class (with probability $1-P_{\text{inf}}$) otherwise. We choose to have more than one exposed class ($k>1$) to allow the distribution of time spent in the latent period to follow an Erlang distribution – a more representative distribution of the latent period than the exponential distribution (e.g., [23,30]). Once a subject has passed through the k exposed classes, they transition into the infectious class. Once a subject is in the infectious class, they may transmit some dose to uncolonised subjects, where β is the effective transmission rate. Fig. 1 provides a graphical representation of this process. In the example considered herein, we use $k=2$ and $\gamma=2$, in order to achieve a mean time between exposure and infectiousness of 1 day (and probability 0.9 of being infectious by day 2) [7], consistent with values reported in [8] on

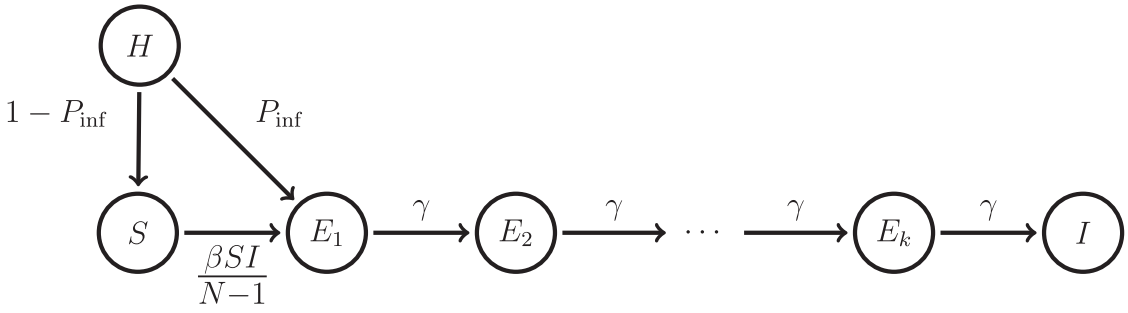

Fig. 1. Diagram illustrating the progression of subjects through the complete model. Subjects begin as Healthy (H), and after being dosed, move to the first Exposed class (E_1) with probability P_{inf}, or otherwise they move to the Susceptible class (S). Once exposed, the subjects pass through k exposed classes ($E_1, \ldots, E_k$), each at rate γ, to reach the Infectious class (I). Once in the infectious class, the subject can transmit the infection to subjects in the susceptible class with effective transmission rate β.